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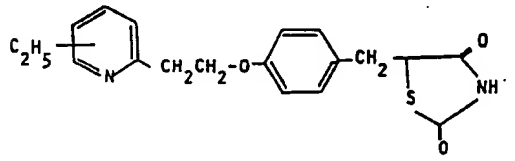
(54) **Thiazolidinedione derivatives, their production and use.**

(57) Thiazolidinedione derivatives of the formula:



or pharmacologically acceptable salts thereof are novel compounds, which exhibit in mammals blood sugar- and lipid-lowering activity, and are of value as a therapeutic agent for diabetes and therapeutic agent for hyperlipemia.

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Thiazolidinedione Derivatives, Their Production and Use

This invention relates to novel thiazolidinedione derivatives, a method of preparing them and antidiabetic agents containing same, which is utilized in the field of medicines.

A variety of biguanide and sulfonylurea derivatives have been used clinically as antidiabetic agents.

However, the biguanides are now scarecely used, because they tend to cause lactic acidosis, and use of the sulfonylureas, though they have strong hypoglycemic activities, requires sufficient precaution, because they cause serious hypoglycemia frequently. Therefore, a new type of antidiabetic agent free from these defects has been desired.

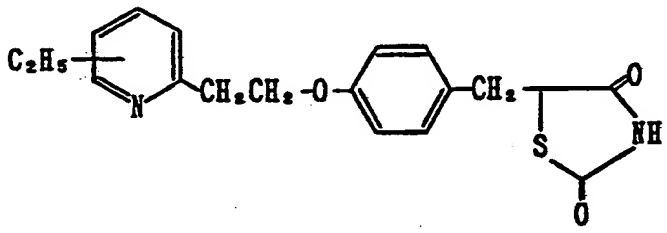
On the other hand, in Japanese Unexamined Patent Publication Nos. 22636/1980 and 64586/1980, Chemical & Pharmaceutical Bulletin, 30, p. 3563 (1982), ibid, 30, p. 3580 (1982), and ibid, 32, p. 2267 (1984), reference is made to a variety of thiazolidinediones having blood glucose and lipid lowering actions. Antidiabetic activity of ciglitazone was also reported in Diabetes, 32, p. 804 (1983). Those compounds, however, have not yet been put to practical use. As the r asons, 1) insufficient activities or/and 2) serious toxicities may be mentioned.

The present inventors synthesized various compounds which are not concretely described in the above-mentioned publications of unexamined patent applications and have made studies on them to find compounds exhibiting potent pharmacological effects with lower toxicity.

The present invention is to provide compounds which can be used practically as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions.

The present invention relates to:

1. A compound of the formula:

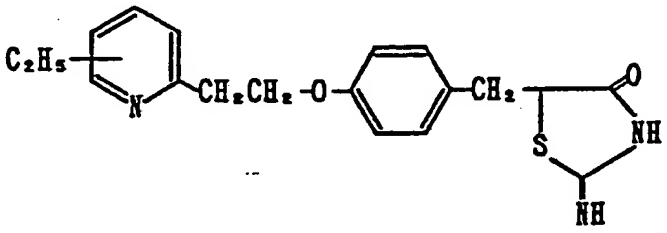


(I)

or a pharmacologically acceptable salt thereof,

2. an antidiabetic agent, which contains as the effective component a compound of the formula (I) or a pharmacologically acceptable salt thereof, and

3. a method of preparing a compound of the formula (I) or a pharmacologically acceptable salt thereof, which comprises hydrolyzing a compound of the formula:



(II)

The compounds representable by the above formula (I) include, specifically stating, the following ones.

5-[4-[2-(3-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(4-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

The compound (I) of this invention contains both basic nitrogen and acid nitrogen in its molecule, and it can be led to a pharmacologically acceptable salt, when desired, by using a suitable acid or base.

Such acid salts are exemplified by mineral salts (e.g. hydrochloride, hydrobromide, sulfate, etc.), organic acid salts (e.g. succinate, maleate, fumarate, malate, tartrate, etc.) and sulfonates (e.g. methanesulfonate, benzenesulfonate, toluenesulfonate, etc.). Such basic salts are exemplified by alkali metal salts e.g. sodium salt, potassium salt, alkaline earth metal salts, e.g. calcium salt, etc. All of these salts can be prepared by per se known means.

The compound (I) of this invention or a pharmacologically acceptable salt thereof exhibits blood-glucose and blood-lipid lowering action with lower toxicity, which can be used as it is or in admixture with a per se known pharmacologically acceptable carrier, excipient or filler as an antidiabetic agent for mammals including man.

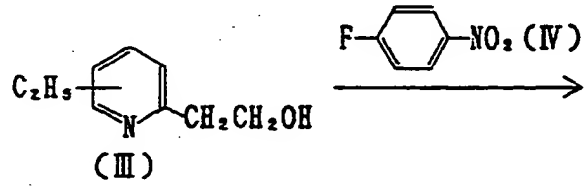
The antidiabetic agent is usually administered orally as tablets, capsules (including soft capsules and microcapsules), powders, granules, etc. and depending on the case, parenterally as injections, suppositories, pellets, etc. Oral administration to an adult patient is desirably 0.05-10 mg/kg body weight/day, and parenterally 0.01-10 mg/kg body weight/day, once daily

or divided into 2-4 times a week.

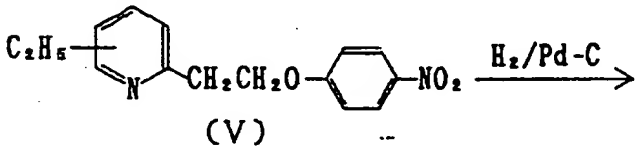
The compound represented by the above mentioned general formula (I) and pharmacologically acceptable salts thereof [hereinafter collectively referred to as "Compound (I)"] can be prepared by subjecting a compound represented by the general formula (II) to hydrolysis. This reaction proceeds advantageously in a proper solvent by employing a mineral acid. The solvent is exemplified by alcohols (e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide, sulfolane, dioxane, tetrahydrofuran, dimethoxyethane, etc., and the mineral acid is exemplified by hydrochloric acid, hydrobromic acid, sulfuric acid, etc. The reaction temperature ranges from 20°C to 150°C. The reaction time is 0.5 - 20 hours.

The compound (I) or a pharmacologically acceptable salt thereof produced as mentioned above can be isolated and purified by conventional means such as concentration, extraction, recrystallization, chromatography, etc.

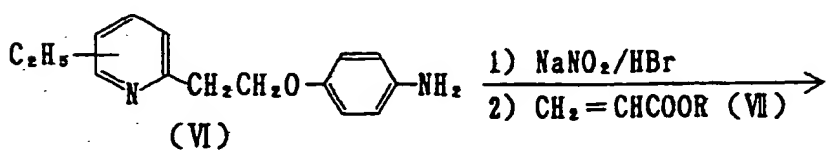
The compound represented by the above-mentioned general formula (II) can be produced by the following reactions:



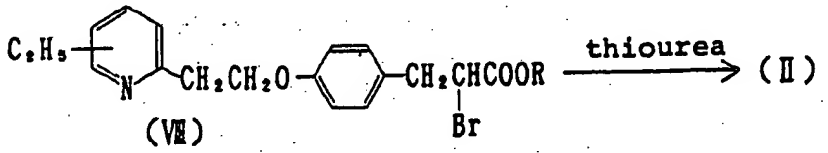
(III)



(V)



(VI)



(Ⅶ)

[wherein R stands for hydrogen or lower alkyl].

The lower alkyl group represented by R is exemplified by (C_{1-4}) ones such as methyl, ethyl, propyl, isopropyl and butyl.

The reaction for producing compound (V) from compound (III) and compound (IV) is conducted in the presence of, for example, sodium hydride. This reaction can be carried out in a solvent e.g. dimethylformamide and tetrahydrofuran at a temperature ranging from -10°C to 30°C. The reaction from compound (V) to compound (VI) can easily be conducted by conventional catalytic reduction employing, for example, palladium-carbon as the catalyst. Compound (VI) may be isolated as the pure product or can be subjected to the subsequent reaction step without isolation and purification. Compound (VIII) can be produced by subjecting compound (VI) to diazotization in the presence of an aqueous solution of hydrobromic acid, then allowing the resultant to react with acrylic acid or its lower alkyl ester (VII) in the presence of a copper catalyst e.g. cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide, etc. (Meerwein arylation). Compound (VIII)

can be purified by e.g. chromatography, and subjected to the subsequent reaction without isolation or purification.

Compound (VIII) is then allowed to react with thiourea to give compound (II). This reaction is carried out usually in alcohols (e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide, sulfolane, etc. The reaction temperature is usually 20 - 180°C, preferably 60 - 150°C. The amount of thiourea to be employed is 1- 2 moles relative to one mole of compound (VIII).

In this reaction, as the reaction proceeds, hydrogen bromide is produced as a by-product, and, for capturing this by-product, the reaction may be conducted in the presence of sodium acetate; potassium acetate, etc., in an amount of usually 1 - 1.5 mole relative to 1 mole of compound (VIII). The resultant compound (II) can be isolated, but may be led to the hydrolysis step directly without isolation:

The compound (I) of the present invention has an excellent blood glucose and lipid lowering activity and is remarkably low in toxicity, which is supported by the following experimental data.

Experimental Examples

1. Blood glucose and lipid lowering activity in mice

To male KKA^{y} mice (8-10 weeks old, 5 mice/group), the test compounds (at three dosage levels) were given as a dietary admixture in CE-2 powdered diet (CLEA Japan) with free access to water for 4 days.

Blood samples were taken from the orbital vein on the 5th day.

Blood glucose and plasma triglyceride (TG) were determined by a glucose oxidase method and by using a commercially available assay kit, Cleantech TG-S (Iatron, Japan), respectively. Based on dose-response curves for blood glucose and plasma TG lowering activity, the effective dose of each test compound in 25% decrease from the control value was calculated as the value of ED_{25} (mg/kg/day). The results are shown in Table 1.

2. Lipid lowering activity in rats

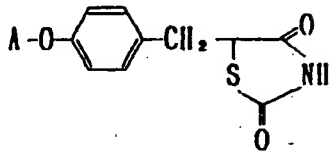
Male Sprague-Dawley rats (7 weeks old, 5 rats/group) were maintained on the laboratory chow (CE-2, CLEA, Japan) with free access to water. All the test compounds (at three dosage levels) suspended in 5% gum arabic solution were

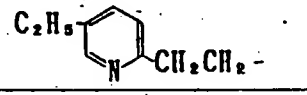
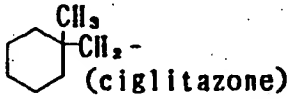
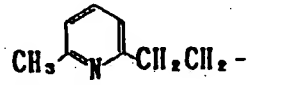
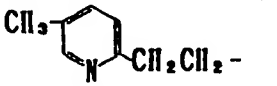
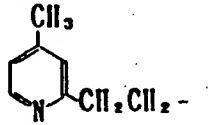
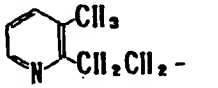
forcedly administered to the animals orally for 4 days. Blood samples were taken from the tail vein on the 5th day. Plasma TG was determined using a commercially available assay kit, Cleantech TG-S (Iatron). Based on dose-response curves for lipid lowering activity, the effective dose of each test compound in 25% decrease from the control value was calculated as the value of ED_{25} (mg/kg/day). The results are shown in Table 1.

3. Two-week toxicity study in rats

Male and female Sprague-Dawley rats (5 weeks old, 5 rats/group) were maintained on the laboratory chow (CE-2, CLEA Japan) with free access to water. All the test compounds suspended in 5% gum arabic solution were forcedly administered orally to the animals for 2 weeks once daily. The dose was 100 mg/kg/day for every test compound. The animals were sacrificed in about 20 hours of fasting after termination of the two-week administration by withdrawing blood samples from the abdominal aorta using heparinized syringes under ether anesthesia. The liver and heart were removed and weighed. Hematology analysis was also carried out using an automatic cell counter. The data represent % increase or decrease from the control value (non-drug treated) as shown in Table 1

Table 1



Compound	A	Blood Glucose (ED_{25})	TG(ED_{25})		Two-weeks toxicity (rat, %)					
					Liver weight		Heart weight		number of erythrocytes	
		mouse	mouse	rat	♂	♀	♂	♀	♂	♀
(I)		6	6	3	-0.7	-3.5	+0.9	-3.9	-3.4	-0.7
(a)	 (ciglitazone)	40	40	70	+6.6*	+10.8*	+13.4*	+4.0	+3.5	-0.2
(b)		4	3	5	+3.8	+10.7**	+19.9**	+17.8**	-2.9	-8.8**
(c)		20	20	—	+1.3	-1.2	+7.2	+3.0	-4.2	-6.0
(d)		20	20	—	+8.8*	+8.4**	+3.3	+7.3*	-3.7	-2.5
(e)		20	20	—	-2.3	+6.6**	+10.9	+9.8*	-8.7*	-7.0**

t-test: *$P < 0.05$; **$P < 0.01$

In Table 1, Compound (I) is a compound under the coverage of the present invention, compounds (a) and (b) are known compounds concretely referred to in the Japanese unexamined Patent Publication No.22636/1980.

While compounds (c), (d) and (e) are not concretely referred to in the above-mentioned patent publication, they are cited for comparison, since they are similar to compound (I) of this invention in their chemical structures. As is apparent from the experimental results given in Table 1, Compound (I) of this invention is superior to the compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared with the compounds (a), (b), (d) and (e). Such an effect as above caused by the introduction of an ethyl group is quite unexpected. Thus, compound (I) of the present invention exhibits excellent hypoglycemic and hypolipidemic acivities, and little toxicity to internal organs and blood even by continuous administration for a long period of time. Therefor, compound (I) is of value as a therapeutic agent for Type II diabetes accompanied by obesity or hyperlipemia in mammals including man.

Example 1

a) To a solution of 2-(5-ethyl-2-pyridyl)ethanol (53.0 g) and 4-fluoronitrobenzene (47.0 g) in DMF (500 ml) was added portionwise under ice-cooling 60% sodium hydride in oil (16.0g). The mixture was stirred under ice-cooling for one hour then at room temperature for 30 minutes, poured into water and extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to give 4-[2-(5-ethyl-2 pyridyl)ethoxy]nitrobenzene as crystals (62.0 g, 62.9%). Recrystallization from ether-hexane gave colorless prisms, m.p. 53-54°C.

b) A solution of 4-[2-(5-ethyl-2-pyridyl)ethoxy]-nitrobenzene (60.0 g) in methanol (500 ml) was hydrogenated at room temperature under one atmospheric pressure in the presence of 10% Pd-C (50% wet, 6.0 g). The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in acetone (500 ml)-methanol (200 ml). To the solution was added a 47% HBr aqueous solution (152 g). The mixture was cooled, to which was added dropwise a solution of $NaNO_2$ (17.3 g) in water (30 ml) at a temperature not higher than 5°C. The whole mixture was stirred at 5°C for 20 minutes, then methyl acrylate (112 g) was added thereto and the temperature was raised to 38°C. Cuprous oxide (2.0 g) was added to the mixture in small portions with vigorous stirring. The reaction mixture was stirred until

nitrogen gas evolution ceased, which was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to leave methyl 2-bromo-3-{4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl}propionate as a crude oil (74.09 g, 85.7%). IR(neat)cm^{-1}:1735. NMR δ(ppm) in $CDCl_3$: 1.21 (3H,t,J=7), 2.60(2H,q,J=7), 3.0 - 3.6(4H,m), 3.66(3H,s), 4.30(2H,t,J=7), 4.3(1H,m),6.7 - 7.5(6H,m), 8.35(1H,d,J=2).

c) A mixture of the crude oil of methyl 2-bromo-3-{4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl} propionate (73.0 g) obtained in b) thiourea (14.2 g), sodium acetate (15.3 g) and ethanol (500 ml) was stirred for 3 hours under reflux. The reaction mixture was concentrated under reduced pressure, and the concentrate was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, to which were added water (200 ml) and ether (100 ml). The whole mixture was stirred for 10 minutes to yield 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2-imino-4-

thiazolidinone as crystals (0.3 g, 523.0%). Recrystallization from methanol gave colorless prisms, m.p. 187-188°C (decomp.). Elemental analysis for $C_{19}H_{21}N_3O_2S$

Calcd: C, 64.20; H, 5.95; N, 11.82.

Found: C, 64.20; H, 5.84; N, 11.73.

d) A solution of 5-{4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl}-2-imino-4-thiazolidinone (23.5 g) in 2N HCl (200 ml) was refluxed for 6 hours. The solvent was evaporated off under reduced pressure, and the residue was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. The crystals (23.5 g, 97.5%) which precipitated were collected by filtration and recrystallized from DMF-H_2O to give 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione as colorless needles (20.5 g, 86.9%), m.p. 183-184°C

Elemental Analysis for $C_{19}H_{20}N_2O_3S$

Calcd: C, 64.02; H, 5.66; N, 7.86.

Found: C, 63.70; H, 5.88; N, 8.01.

e) To a suspension of 5-{4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl}-2,4-thiazolidinedione (356 mg) in methanol (10 ml) was added 28% sodium methylate/methanol solution (0.2 g) to make a solution. This solution was concentrated and diluted with ethyl ether to yield crystals.

The crystals were collected by filtration and recrystallized from methanol-ethanol to give the sodium salt of 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benxyl}-2,4-thiazolidinedione as colorless crystals (298 mg, 78.8%), m.p. 262-263°C (decomp.).

Elemental analysis for $C_{19}H_{19}N_2O_3SNa$:

Calcd. : C,60.31; H,5.06; N,7.40

Found : C,60.20; H,5.07; N,7.52

Example 2

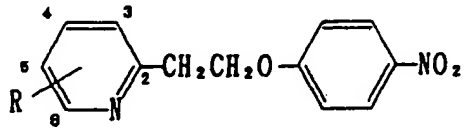
(1)	5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione	100 g
(2)	Lactose	50 g
(3)	Corn starch	15 g
(4)	Carboxymethyl cellulose calcium	44 g
(5)	Magnesium stearate	1 g
		210 g

The whole amounts of (1), (2) and (3) and 30 g of (4) were kneaded with water and dried in vacuo, followed by granulation. With the resultant granules were mixed 14 g of (4) and 1 g of (5) and the whole mixture was tableted with a tableting machine to give 1000 tablets 8 mm in diameter and each containing 100 mg of (1).

Reference Example 1

The compounds listed in Table 2 were prepared in accordance with Example 1-a).

Table 2



R	mp	Recrystalization solvent	yield
3-CH_3	116-117℃	ethyl acetate-hexane	62.9%
4-CH_3	73-74℃	ethyl acetate-hexane	57.3%
5-CH_3	97-98℃	ethyl acetate-hexane	72.3%

Reference Example 2

In accordance with Example 1-b), the following compounds were prepared.

Methyl 2-bromo-3-{4-[2-(3-methyl-2-pyridyl)ethoxy]phenyl} propionate; IR(Neat)cm^{-1}: 1735. NMR δ(ppm) in $CDCl_3$: 2.34(3H,s), 3.10(1H,dd, J=14 and 7), 3.25(2H,t,J=6), 3.38(1H,dd, J=14 and 7), 3.67(3H,s), 4.29(1H,t,J=7), 4.37(2H,t,J=6), 6.8-7.5(6H,m), 8.35(1H,dd, J=5 and 2).

2-Bromo-3-{4-[2-(4-methyl-2-pyridyl)ethoxy]phenyl} propionic acid methyl ester ; IR(Neat)cm^{-1}: 1735.
NMR δ(ppm) in $CDCl_3$: 2.30(3H,s), 3.10(1H, dd, J=14 and 7), 3.26(3H,t,J=7), 3.37(1H,dd, J=14 and 7), 3.67(3H,s), 4.30(3H,t,J=7), 6.7-7.36(6H,m), 8.37(1H,d,J=6)

Reference Example 3

A solution of 4-[2-(5-methyl-2-pyridyl)ethoxy] nitrobenzene (15.0 g) in methanol (150 ml) was subjected to catalytic reduction under 1 atmospheric pressure in the presence of 10% Pd-C (50% wet, 2.0 g). The catalyst was filtered off, and the filtrate was concentrated to give 4-[2-(5-methyl-2-pyridyl)ethoxy]aniline as crystals (12.3 g, 92.5%). Recrystallization from ethyl acetate-hexane gave colorless prisms, m.p. 74-75°C.

Elemental analysis for $C_{14}H_{16}N_2O$:

Calcd.:	C, 73.66;	H, 7.06;	N, 12.27.
Found:	C, 73.84;	H, 7.17;	N, 12.06.

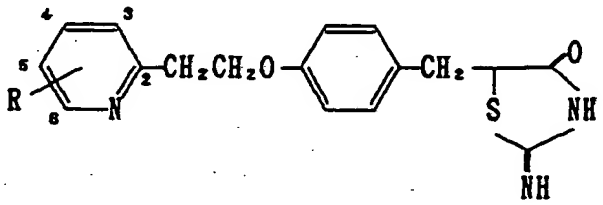
Refer nce Example 4

To a mixture of 4-[2-(5-methyl-2-pyridyl)ethoxy]aniline (12.0 g), 47% aqueous HBr solution (36.5 g) and methanol (40 ml)-acetone (80 ml) was added dropwise a solution of $NaNO_2$ (4.0 g) in water (10 ml) at 5°C or below. The whole mixture was stirred at 5°C for 20 minutes, then methyl acrylate (27.0 g) was added thereto and the temperature was raised to 38°C. Cuprous oxide (1.0 g) was added to the mixture in small portions with vigorous stirring. After nitrogen gas evolution had ceased, the reaction mixture was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to leave methyl 2-bromo-3-{4-[2-(5-methyl-2-pyridyl)ethoxy]phenyl}-propionate as a crude oil (17.5 g, 87.5%). IR(Neat)cm^{-1}: 1735. NMR δ(ppm) in $CDCl_3$: 2.27(3H,s), 3.10(1H,dd,J=14 and 7), 3.22(2H,t, J=6), 3.38(1H,dd,J=14 and 7),3.66(3H,s), 4.29(2H,t, J=6), 4.32(1H,t,J=7), 6.7-7.5(6H,m), 8.34(1H,d,J=2).

Reference Example 5

The compounds listed in Table 3 were prepared in accordance with Example 1-c).

Table 3

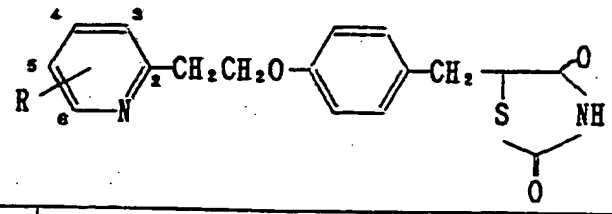


R	mp (decomp.)	Recrystalization solvent	yield
3 $-CH_3$	230-231℃	chloroform-methanol	75.5%
4 $-CH_3$	190-191℃	methanol	48.0%
5 $-CH_3$	203-204℃	chloroform-methanol	58.2%

Reference Example 6

The compounds listed in Table 4 were prepared in accordance with Example 1-d).

Table 4



R	mp	Recrystalization solvent	yield
3 $-CH_3$	210-211℃	DMF-water	65.7%
4 $-CH_3$	178-179℃	chloroform-methanol	75.3%

Reference Example 7

A mixture of 2-imino-5-{4-[2-(5-methyl-2-pyridyl) ethoxy]benzyl}-4-thiazolidinone (8.0 g), 2N HCl (80 ml) and ethanol (80 ml) was refluxed for 16 hours. The reaction solution was neutralized with a saturated aqueous solution of sodium hydrogencarbonate to yield crystals. The crystals were collected by filtration and re-crystallized from ethanol to give 5-{4-[2-(5-methyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione as colorless prisms (7.0 g, 87.5%), m.p. 192-193°C.

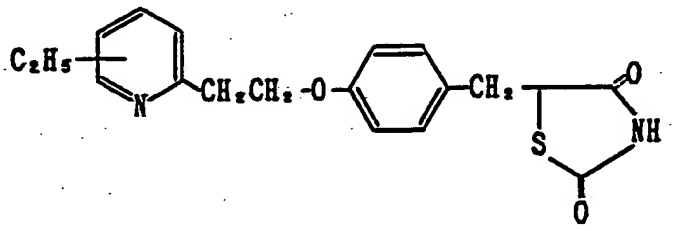
Elemental Analysis for $C_{18}H_{18}N_2O_3$:

Calcd.: C,63.14: H,5.30; N,8.18

Found : C,63.22; H,5.40: N, 8.11

Claims:

1. A compound of the formula:

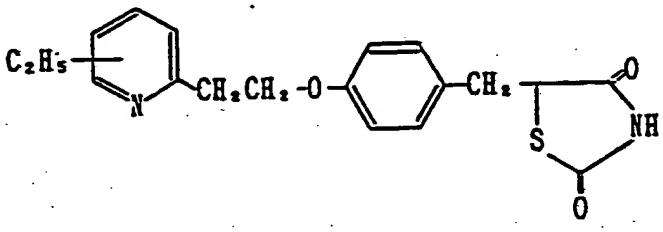


or pharmacologically acceptable salts thereof.

2. A compound as claimed in Claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione.

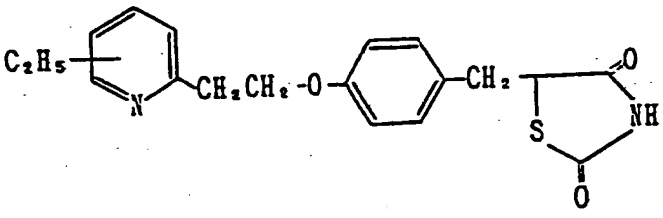
3. A compound as claimed in Claim 1, wherein the compound is a sodium salt of 5-{4-[2-(5-ethyl-2-pyridyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

4. An antidiabetic agent, which contains as the effective component a compound of the formula:

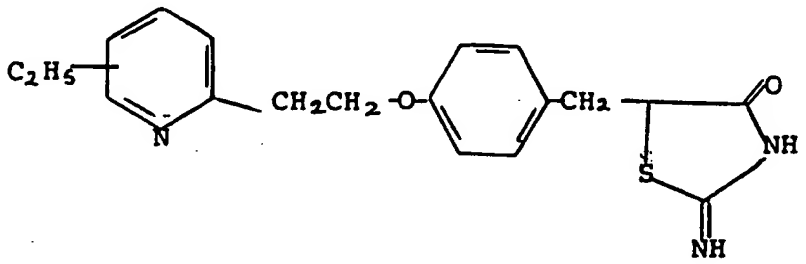


or a pharmacologically acceptable salt thereof.

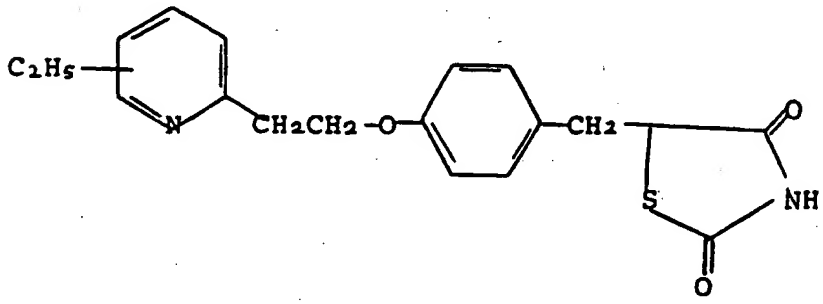
5. A method of preparing a compound of the formula:



or a pharmacologically acceptable salt thereof, which comprises hydrolyzing a compound of the formula:



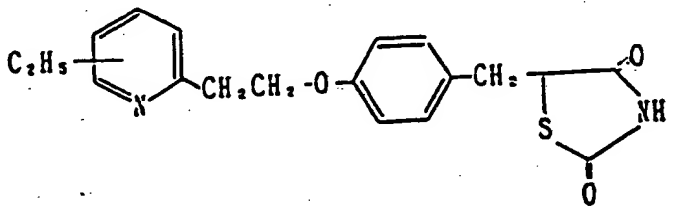
6. The use of a compound of the formula:



for the production of a therapeutic agent for diabetes and therapeutic agent for hyperlipemia.

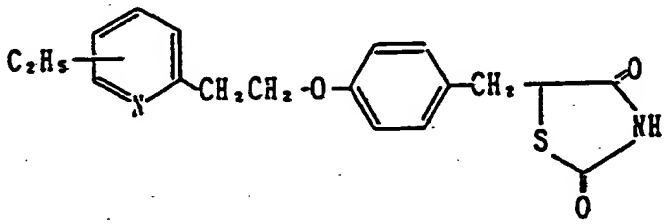
AUSTRIAN CLAIMS

1. A compound of the formula:

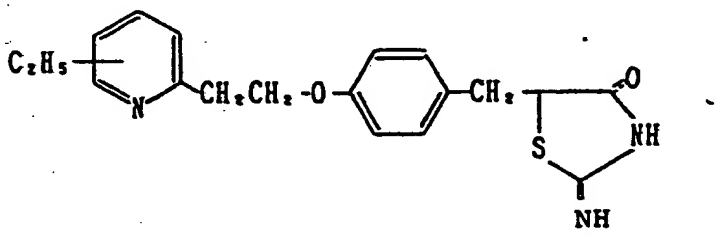


or pharmacologically acceptable salts thereof.

2. A method of preparing a compound of the formula:



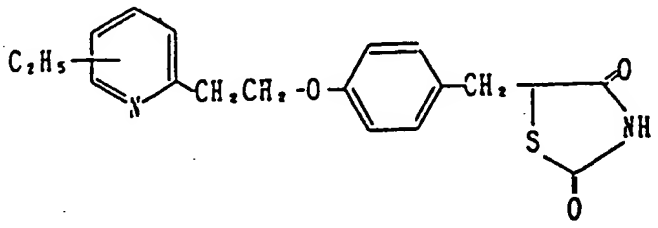
or a pharmacologically acceptable salt thereof, which comprises hydrolyzing a compound of the formula:



3. A method of preparing a compound as claimed in Claim 2, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxyl]benzyl}-2,4-thiazolidinedione.

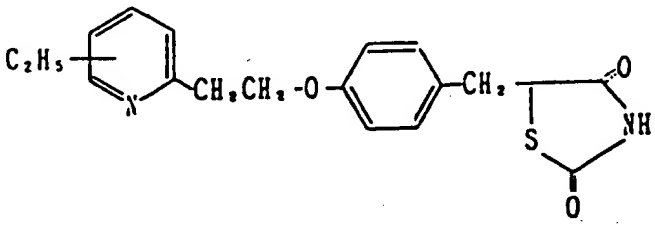
4. A method of preparing a compound as claimed in Claim 2, wherein the compound is a sodium salt of 5-{4-[2-(5-ethyl-2-pyridyl)-ethoxy]benzyl}-2,4-thiazolidinedione.

5. An antidiabetic agent, which contains as the effective component a compound of the formula:



or a pharmacologically acceptable salt thereof.

6. The use of a compound of the formula:



for the production of a therapeutic agent for diabetes and therapeutic agent for hyperlipemia.

0193256

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 86 30 0220

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl 4)
A	EP-A-0 008 203 (TAKEDA)		C 07 D 417/12 A 61 K 31/44 A 61 K 31/425
A	CHEMICAL ABSTRACTS, vol. 99, no. 23, 5th December 1983, pages 744-745, no. 194854u, Columbus, Ohio, US; T. SOHDA et al.: "Antiulcer activity of 5-benzylthiazolidine-2,4-dione derivatives", & CHEM. PHARM. BULL. 1983, 31(2), 560-9		
P,A	EP-A-0 155 845 (TAKEDA)		

TECHNICAL FIELDS SEARCHED (Int. Cl 4)

C 07 D 417/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	06-05-1986	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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